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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/938,816	08/27/2001	Jacobus M. Lemmens	ADP-016US2	1906

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EXAMINER
GOLLAMUDI, SHARMILA S

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 05/05/2003

11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/938,816	LEMMENS ET AL.	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9/10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt of Amendment A and Information Disclosure received on February 4, 2003 and Supplementary Information Disclosure received on March 38, 2003 is acknowledged. Claims 1-2 and 4-33 are included in the prosecution of this application. Claim 3 has been cancelled.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejection of claims 1-2, 4-9, 11, 14-18, and 22 under 35 U.S.C. 103(a) as being unpatentable over Davison et al (4879303) is maintained.

Davison et al teach the pharmaceutically acceptable salts of amlodipine such as amlodipine maleate in a pharmaceutical composition for treating angina and hypertension. The reference discloses the preferred pH of the composition to be close to that of the blood pH of 7.4 because it can be readily biocompatible (col. 2, lines 22-31). The pH of amlodipine maleate is taught to be 4.8 (Table 1). The active in formed into a tablet or capsule containing microcrystalline cellulose and dibasic calcium phosphate (col.2, lines 50-60). Davison et al teach the use of sodium starch glycollate in the pharmaceutical composition (Table 3). Davison et al teach the method of compressing the composition into a tablet form and the method of filling the capsules.

Davison et al do not teach the instant pH of the composition.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to adjust the pH of the composition with known pH adjusting agents

such as sodium glycollate as taught by Davison et al to have a pH closer to that of the blood to improve biocompatibility. Further, Davison discloses the pH of the instant (4.8) and the use of dibasic calcium phosphate in the composition; therefore a skilled artisan would recognize that this combination would yield a pH within the recited range.

Response to Arguments

Applicant argues that the examiner has misread Davison and that Davison describes a characteristic by which salt is selected and not a criterion for forming a solid pharmaceutical. Applicant argues that calcium phosphate and sodium glycollate does not inherently form a pH within the applicant's range as argued by the examiner. It is argued that the pH depends on the type of calcium phosphate as well as the relative amounts of the calcium phosphate. It is further argued that the brands and grades of the buffer will affect the pH.

Applicant's arguments have been fully considered but they are not persuasive. Firstly the examiner points to Table 2 on column 4 wherein Davison clearly teaches a tablet containing amlodipine maleate. Secondly, the examiner points out that points page 7 of applicant's response wherein the applicant admits that the pH of the composition has little effect on the stomach and rather the composition is modified by the pH of the stomach. It would appear from this statement that the pH of the composition is in fact not critical. One of ordinary skill in the art would be motivated to select the proper pH based on Davison' teachings on column 2, line 47 wherein he states that good stability in the solid state is very important for tablets and capsules. Thus, one can come to the conclusion that a solid state should have a proper pH, which

contributes to stability. Additionally, Davison teaches that besylate and maleate remained anhydrous minimizing the risk of intrinsic breakdown on column 3, lines 20-29. Further, one skilled in the art would be motivated to select a pH closer to that of the blood since Davison states that compositions with this range are biocompatible. Davison teaches the addition of dibasic calcium phosphate to each of the salts, which would provide for a pH within the given range. The applicant merely argues that this pH is not inherent without evidence to support such as statement. The examiner points out that both the prior art and the instant claims recite the calcium phosphate. If the amount and type of buffer used are critical to the invention, the applicant fails to incorporate this into the dependent claims. The examiner provides Methods in Enzymology, page 143 as art of interest. The use of a phosphate buffer can only yield a minimum pH range of 5.7 and a maximum pH of 8. This range is close to that of claimed range and with the teachings of Davison in which he states that it is desirable to have the pH close to that of blood, it is the examiner's position that this range is implicitly taught.

Applicant argues that the present inventors have discovered a solution to the stability problem of the formation of the derivative aspartate and nothing in Davison addresses this problem. Applicant argues that the specification provides unexpected results.

Applicant's arguments have been fully considered but they are not persuasive. Firstly the examiner points out that Davison does discuss stability problems as discussed above. Although Davison does not explicitly state the conversion of maleate to aspartate, Davison teaches instability to include chemical breakdown, which

encompasses the formation of aspartate. The examiner points out that the upper range studied by the applicant is 6.13 wherein claimed upper range 6.8, which is close to pH of blood. Davison merely states that the pH should be close to that of blood. Secondly, the examiner points out that the unexpected results are not commensurate in scope of the claims. The examples recite specific tablet formulations, whereas the claims claim a broad scope of formulations. Additionally applicant argues that the amount and type of calcium buffer effect the pH; however claims do not recite any of these limitations. Further, the unexpected results are not a direct comparison with the closest prior art as discussed in the interview of January 29, 2003. Applicant argues that Davison does not provide a precise formulation; therefore applicant does not have to provide data. The examiner again points out that Davison teaches the amlodipine maleate with instant excipients. This reads on the broad claims since applicant claims amlodipine maleate and excipients. Davison states that compositions with a pH near blood are readily biocompatible. Therefore, providing direct motivation to alter the pH of amlodipine maleate. Lastly, the examiner points out that applicant's arguments are based on features that are not recited in the claims, i.e. stability of the composition, aspartate formation, or the use of an acidic medium to maintain stability.

Rejection of claims 12-13 under 35 U.S.C. 103(a) as being unpatentable over Davison et al (4879303) in view of EP 0089167 is maintained.

As set forth above, Davison et al teach a pharmaceutical composition containing amlodipine maleate.

Davison et al do not teach the amount of amlodipine maleate.

EP teaches a pharmaceutical composition containing amlodipine and preferable its salt form, amlodipine maleate. Tablets and capsules contain 1 to 10mg preferably to treat cardiac condition (pg. 7).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the instant recited range of active since EP teaches this amount to effectively treat cardiac conditions.

Response to Arguments

Applicant does not argue the merits of the rejection rather he discusses the merit of Davison which have been discussed above.

Rejection of claims 10 and 19-20 under 35 U.S.C. 103(a) as being unpatentable over Davison et al (4879303) in view of Sherwood et al (5585115) is maintained.

As set forth above, Davison et al teach a pharmaceutical composition containing amlodipine maleate.

Davison et al do not teach a coated tablet or specify the type of granulation (wet/dry).

Sherwood et al teach a method of improving compressibility in tablets using microcrystalline cellulose. Sherwood discloses the three general methods of preparing solid dosage forms: dry granulation, direct compression, and wet granulation (col. 1, lines 64-67). Sherwood discloses that the method depends on the drug and excipients. Lastly Sherwood teaches the optional use of a hydrophobic coating to provide a sustained release (col. 12, lines 60-66).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Davison et al and Sherwood et al since Sherwood teaches the art of tabletting and using a granulation method depending on the drug and excipients. Further, Sherwood teaches the use of tablet coatings to provide for sustained release.

Response to Arguments

Applicant does not argue the merits of the rejection rather he discusses the merit of Davison which have been discussed above.

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Davison et al (4879303) in view of Sherwood et al (5585115) in further view Schobel (4687662).

As set forth above, Davison et al teach a pharmaceutical composition containing amlodipine maleate. Sherwood et al teach the method of making a solid dosage form.

The references do not specify the particle size of the active.

Schobel discloses a therapeutic effervescent composition. Schobel teaches the generally the preferred particle size when tabletting a solid dosage form. The reference discloses a particle size less than 100 microns has processing problems such as poor mixing and compressibility. (Col. 4, lines 31-45)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use particle sizes above 100 microns for a solid dosage form since Schobel teaches fine particles less than 100 microns tend to cause processing problems such as poor mixing and compressibility. One of ordinary skill in the art would

expect similar results since Schobel teaches the particle size for making a solid dosage form.

Response to Arguments

Applicant does not argue the merits of the rejection rather he discusses the merit of Davison which have been discussed above.

Rejection of claims 23-27 under 35 U.S.C. 103(a) as being unpatentable over Davison et al (4879303) in view Schobel (4687662) is maintained. New claims 32-33 are also rejected.

As set forth above, Davison et al teach a pharmaceutical composition containing amlodipine maleate.

Davison et al do not specify the particle size.

Schobel discloses a therapeutic effervescent composition. Schobel teaches the generally the preferred particle size when tabletting a solid dosage form. The reference discloses a particle size less than 100 microns has processing problems such as poor mixing and compressibility. (Col. 4, lines 31-45)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use particle sizes above 100 microns for a solid dosage form since Schobel teaches fine particles less than 100 microns tend to cause processing problems such as poor mixing and compressibility. One of ordinary skill in the art would expect similar results since Schobel teaches the particle size for making a solid dosage form.

Response to Arguments

Applicant does not argue the merits of the rejection rather he discusses the merit of Davison which have been discussed above.

Claims 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davison (4879303) in view of Takatsuka et al (6471946).

As set forth above, Davison et al teach a pharmaceutical composition containing amlodipine maleate. Davison teaches adjusting the pH of the composition to that of blood or close to blood pH for biocompatibility. Davison teaches the use of excipients for compression aids such microcrystalline cellulose.

Davison does not teach the use of an acid pH-adjusting agent.

Takatsuka teaches an oral composition. The reference teaches conventional pH adjusting agents are citric acid, phosphoric acid, malic acid, and maleic acid.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use acid pH adjusting agents in Davison et al since Davison clearly teaches the use buffering agents to alter the pH so that the it will be biocompatible. One would be motivated to do so since Davison incorporates excipients that are basic, which might increase the pH beyond that of the pH of blood; therefore one would use an acidic pH-adjusting agent to lower the pH closer to blood.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is (703) 305-2147. The examiner can normally be reached on M-F (7:30-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jose Dees can be reached on (703) 308-4628. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SSG

April 24, 2003

MICHAEL G. HARTLEY
PRIMARY EXAMINER